REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-5, 8, 13, 16-19, 22, and 33-40 are pending in this application and presented for examination. Claims 6, 7, 9-12, 14, 15, 20, 21, and 23-32 have been canceled without prejudice or disclaimer. Claims 1, 8, 13, and 19 have been amended. Claims 33-40 are newly added. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

Claims 1, 8, 13, and 19 have been amended. Support for the amendments to the claims is found, for example, from page 11, line 33 to page 12, line 5. Claims 33-40 are newly added. Support for the new claims is found, for example, on page 12, lines 5-13, on page 23, lines 9-14, and from page 25, line 34 to page 26, line 2. Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendments to the claims and the new claims be entered.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-5, 8, 13, 16-19, and 22 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that "the specification, while being enabling for 'inhibiting' [a] malignant cell phenotype in an animal, does not reasonably provide enablement for 'preventing' the same." Further, the Examiner alleges that "the specification, while being enabling for increasing efficacy of an antimalignant modality, treating cancer, or inhibiting [a] malignant cell phenotype in an animal for a specific 'low dose' range, such as 10^{-14} M to 10^{-10} M, does not reasonably provide enablement for other unspecified 'low dose' range[s]."

In order to expedite prosecution, Applicants have amended claims 1 and 13 to delete the term "preventing" from the claims. However, as a skilled artisan will readily recognize, the term "inhibiting" includes preventing, and/or treating, such as prophylactic treatment and/or decreasing a malignant cell phenotype.

Applicants have also amended claims 1, 8, 13, and 19 to recite that the low dose of a nitric oxide mimetic is 3 to 10,000 fold lower than a dose of the nitric oxide mimetic that produces vasodilation. Applicants submit that the specification discloses that a "low dose" in accordance with the present invention refers to an amount of a nitric oxide mimetic lower than that which produces a systemic effect (*e.g.*, a lowering of blood pressure). For example, as set forth from page 11, line 24 to page 12, line 5 of the specification:

> [I]t is known that administration of nitric oxide or compounds which deliver nitric oxide to human beings at doses conventionally employed to treat cardiovascular conditions (i.e. GTN at 0.2 mg/h or greater) by vasodilation can provoke powerful vasodilator responses as well as development of drug tolerance against GTN upon repeated administration. Such administration is often accompanied by a number of undesirable side effects including headache, flushing and hypotension. In contrast, preferred doses of nitric oxide mimetic administered in the present invention to inhibit and prevent a malignant cell phenotype are lower, preferably at least 3 to 10,000-fold lower, more preferably at least 100- to at least 10,000-fold lower than those typically used in other therapeutic applications such as vasodilation and thus do not induce tolerance to the NO mimetic as quickly nor undesirable side effects.

Further, as shown in Table 1 on pages 13-14 of the specification, for nitric oxide mimetics conventionally used to alter properties in the circulation (*e.g.*, systemic indications such as treating congestive heart failure, angina pectoris, hypertension, and the like), a low dose according to the present invention is less than the amount for such systemic conventional use. Thus, one of ordinary skill in the art would know, or easily be able to ascertain, a low dose suitable for the instant invention of a nitric oxide mimetic used in known systemic therapeutic applications such as vasodilation. One of ordinary skill in the art would also be able to ascertain, using routine methods, a low dose suitable for the instant invention of any given NO mimetic. For example, a low dose of a nitric oxide mimetic according to the present invention can easily

be determined by titration methods routinely used in the art. By monitoring the titration end point, such as a systemic effect, a low dose of a nitric oxide mimetic can be determined.

In addition, Applicants assert that one of ordinary skill in the art would know of routine methods for the determination of a dose of any nitric oxide mimetic required for vasodilation. For example, a skilled artisan could easily measure the mean arterial pressure before and after the administration of different doses of any nitric oxide mimetic in a rat model system. The minimum dose to significantly decrease the mean arterial pressure (*i.e.,* produce vasodilation) could then be used to calculate the low dose for that particular nitric oxide mimetic for use in the present invention. A skilled artisan could then perform a routine titration analysis of different amounts of the mimetic in the low dose range to determine the most effective dosage for inhibiting a malignant cell phenotype, increasing the efficacy of an antimalignant modality, and treating cancer. As such, Applicants submit that one of ordinary skill in the art would know, or easily be able to ascertain, a low dose suitable for the instant invention based on methods well-known in the art and the teachings of the specification. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

Moreover, Applicants have added new claims 33, 35, 37, and 39 to recite that the low dose of a nitric oxide mimetic to be administered ranges from between about 10^{-14} M to about 10^{-6} M for inhibiting a malignant cell phenotype, increasing the efficacy of an antimalignant modality, and treating cancer. Applicants submit that in the Office Action, the Examiner conceded that the specification provides enablement for methods for inhibiting a malignant cell phenotype, increasing the efficacy of an antimalignant therapeutic modality, and treating cancer for a low dose of a nitric oxide mimetic, such as 10^{-14} M to 10^{-10} M. However, Applicants assert that the specification also provides enablement for administering a nitric oxide mimetic at a low dose ranging from between about 10^{-10} M to about 10^{-6} M. For example, administration of low doses of either 10^{-11} M GTN, 10^{-10} M SNP, 10^{-8} M SNP, or 10^{-7} M GTN to hypoxic cancer cells were effective at inhibiting their invasive ability (*see,* page 23, lines 6-14). Further, experiments examining the ability of low doses of nitric oxide mimetics to decrease the resistance of breast cancer cells to doxorubicin demonstrated that "hypoxic cancer cells treated with 10^{-6} M and 10^{-10} M GTN had lower doxorubicin survival rates as compared to untreated

hypoxic cells" (*see,* from page 25, line 26 to page 26, line 7). As such, Applicants assert that the specification provides enablement for administering low doses of a nitric oxide mimetic between about 10^{-14} M to about 10^{-6} M. Therefore, Applicants respectfully request that the Examiner allow these new claims.

III. REJECTION UNDER 35 U.S.C. § 102(a)

Claims 1, 3, and 4 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Umansky *et al.* (*International J. of Oncology*, 16:109-117). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In response, Applicants submit a Declaration by the inventors, Michael A. Adams, Charles H. Graham, Jeremy P. W. Heaton, and Lynne-Marie Postovit, pursuant to 37 C.F.R. § 1.131. The Declaration provides evidence that unequivocally establishes that Applicants conceived of and reduced to practice the claimed invention prior to the date that the journal issue containing the Umansky *et al.* reference was available to the public, *i.e.,* December 23, 1999. The front page of the journal issue with the "received on" date is also attached hereto for the Examiner's convenience (Exhibit A).

Under 37 C.F.R. § 1.131:

> *37 CFR 1.131. Affidavit or declaration of prior invention.*
> (a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. The effective date of a U.S. patent, U.S. patent application publication, or international application publication under PCT Article 21(2) is the earlier of its publication date or date that it is effective as a reference under 35 U.S.C. 102(e). Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country.

Applicants assert that the Declaration establishes invention of the subject matter of the rejected claims prior to the effective date of the reference. As such, the filing of this

Declaration removes Umansky *et al.* as prior art against the present application. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

IV. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 2, 5, 8, 13, 16-19, and 22 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Umansky *et al.* in view of U.S. Patent Publication No. 2001/0038832 ("Bonavida *et al.*") and Chemical Abstracts 129:36441 ("*Chem. Abstracts*"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As discussed above, the filing of the Declaration under 37 C.F.R. § 1.131 removes Umansky *et al.* as prior art against the present application. Further, the Declaration also removes Bonavida *et al.* as prior art against the present application, as Applicants conceived of and reduced to practice the claimed invention prior to the priority date of Bonavida *et al.*, *i.e.,* April 11, 2000. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

As the filing of the above-mentioned Declaration removes Umansky *et al.* and Bonavida *et al.* as prior art against the present application, Applicants assert that *Chem. Abstracts* fails to teach or suggest the present invention. *Chem. Abstracts* discloses the use of GTN to enhance circulation to a target tissue by increasing blood flow into the tissue, thereby causing a vasodilatory response. For example, *Chem. Abstracts* teaches the administration of microspheres and a drug at the time of ***maximum vasodilation*** caused by GTN administration. By contrast, the present invention provides for administration of a nitric oxide mimetic at low doses that are "at least 3 to 10,000-fold lower, more preferably at least 100- to at least 10,000-fold lower than those typically used in other therapeutic applications such as vasodilation and thus do not induce tolerance to the NO mimetic as quickly nor undesirable side effects" (page 11, line 35 to page 12, line 5). As such, because *Chem. Abstracts* discloses the use of GTN for eliciting a ***maximum*** vasodilatory response, one of skill in the art would not have been motivated to modify its teachings to arrive at the present invention. Furthermore, one of skill in the art would not have expected, at the time of the present invention, that the use of nitric oxide

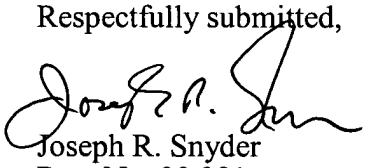
mimetics at such lower doses as is presently taught and claimed would be successful. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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